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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 33/24, 31/445, 31/44 // (A61K 33/24, 31:445) (A61K 31/445, 31:44)

A1

(11) International Publication Number: **WO 97/02039**

(43) International Publication Date: 23 January 1997 (23.01.97)

(21) International Application Number: PCT/EP96/02493

(22) International Filing Date: 7 June 1996 (07.06.96)

(30) Priority Data:
9513551.3 4 July 1995 (04.07.95) GB

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(81) Designated States: JP, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: ANTIBACTERIAL SYNERGISTIC COMPOSITION COMPRISING RIFABUTIN

(57) Abstract

Pharmaceutical anti-bacterial synergistic compositions against *Helicobacter pylori*, containing rifabutin and a proton pump inhibitor or a bismuth preparation.

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ANTIBACTERIAL SYNERGISTIC COMPOSITION COMPRISING RIFABUTIN

The present invention relates to anti-bacterial pharmaceutical compositions against *Helicobacter pylori* and to their preparation.

Helicobacter pylori plays a main role in the pathogenesis of gastritis and peptic ulcer.

Known treatments include the use of amoxicilin or other antibacterial agents in dual or triple combination with other drugs, such as bismuth preparations, metronidazole, tinidazole or with proton pump inhibitors, e.g. omeprazole. Such combinations have a relatively short duration of action and require high doses and repeated administrations (3-4 times per day) owing to the pharmacokinetics or the low antibacterial activity of the antibiotic and its limited stability in the stomach.

We have discovered that a very effective treatment can be achieved by administration of a synergistic composition.

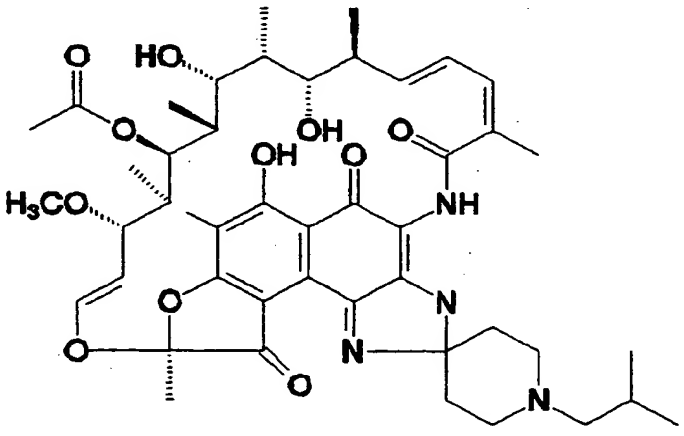
The present invention provides a pharmaceutical composition suitable for use in the treatment of a *Helicobacter pylori* infection, which composition comprises:

(I) rifabutin; and

(II) a proton pump inhibitor or a bismuth preparation in a quantity producing a synergistic activity against *Helicobacter pylori*.

Rifabutin is the generic name of a chemical compound 4-deoxo-3,4-[2-spiro(N-isobutyl-4-piperidyl)-2,5-dihydro-1H-imidazo]-rifamycin S. Depending on the system used to name a chemical compound, it may also be identified as 6,9-dihydro-5,17, 19,21-tetrahydroxy-8,9-[2-spiro-(N-isobutyl-4-piperidyl)-2,5 -dihydro-1H-imidazo]-23-methoxy -2,4,12,16,18,20,22-heptamethyl-6-oxo-2,7-(epoxypentadeca-[1,11,13]-trienimino) naphthol[2,1]-b furan-1,11-(2H)-dione-21-acetate; or (9S,12E, 14S,15R,16S, 17R,18R,19R,20S, 21S, 22E,24Z)-6,16,18,20-tetrahydroxy-1'-isobutyl-14-methyloxy-7,9,15,17,19,21,25-heptamethyl-spiro[9,4-(epoxypentadeca[1,11,13]trienimino-2H-furo[2',3',7,8]naphth[1,2-d]imidazole-2,4'-piperidine-5,10,26,(3H,9H)-trione-16-acetate.

Rifabutin has the structural formula



Molecular formula: $C_{46}H_{62}N_4O_{11}$

Molecular Weight: 847.12

The preparation of rifabutin is described in U.S. Patent 4,219,478 issued on August 26, 1980. Rifabutin is a red violet powder soluble in chloroform and methanol, and very slighly soluble in water; it has a melting point of 148°C-156° (with decomposition).

A proton pump inhibitor is typically omeprazole, lansoprazole, leminoprazole, pantoprazole or robeprazole; a bismuth preparation is typically bismuth subsalicyclate or bismuth subcitrate sol (dried).

The pharmaceutical composition of the invention may further comprise a pharmaceutically acceptable carrier or diluent.

The pharmaceutical composition according to the present invention shows an excellent antibacterial activity, good oral bioavailability and stability at low pH, and it is therefore suited for the treatment of *Helicobater pylori* infections. It was found that the activity of the composition of the invention is greater than the sum of the individual components. A noticeable antibacterial synergistic effect is evident.

A pharmaceutical composition according to the invention possesses a good activity against *Helicobacter pylori* at small doses, which are insufficient when the components are used individually. Consequently, the combination of the two components according to the invention is more effective in the treatment of diseases caused by *Helicobacter pylori*, because it possesses a better therapeutic value than the individual antibiotic.

In addition, antibacterials should not be used as monotheraphy to avoid the emergence of resistant strains. This is particularly important for long term therapy.

The invention further provides a process for preparing the above mentioned composition, which process comprises mixing:

(I) rifabutin;

(II) a proton pump inhibitor or a bismuth preparation in a quantity producing a synergistic activity against *Helicobacter pylori*; and

(III) optionally, a pharmaceutically acceptable carrier or diluent.

Suitable carriers or diluents are those conventionally used in pharmaceutical preparations. For example for tablets or capsules the carrier or diluent commonly comprises starches and binders and/or lubricants.

The present invention also provides a pharmaceutical composition as defined above for use in the treatment of a disease caused by Helicobacter pylori.

The two components may be mixed immediately prior to administration. Then they be presented in a form suitable for combined administration in the treatment of disorders caused by *Helicobacter pylori*. The present invention therefore also provides products comprising:

(I) rifabutin; and

(II) a proton pump inhibitor or a bismuth preparation in a quantity producing a synergistic activity against *Helicobacter pylori*;

as a combined preparation for simultaneous, separate or sequential use in the treatment of a *Helicobacter pylori* infection.

The daily doses of individual components in compositions according to the invention are lower as compared to the active doses of the individual components, when used without the other component. The weight ratio of rifabutin to proton pump inhibitor or bismuth preparation is generally from 1:100 to 100:1. Where the composition of the invention comprises rifabutin and a proton pump inhibitor, the weight ratio of rifabutin:proton pump inhibitor is typically from 25:1 to 5:1. Where the composition comprises rifabutin and a bismuth preparation, the weight ratio of rifabutin:bismuth preparation is typically from 1:10 to 10:1. Typically, for adults (70 kg) the daily doses of rifabutin ranges from 100 to 1000 mg, preferably from 200 to 500 mg, more preferably 300 mg.

The daily dose of the proton pump inhibitor is from 1 mg to 1000 mg, preferably from 10 to 100 mg and the daily dose for the bismuth preparation is from 50 mg to 5000 mg, preferably from about 50 mg to about 1000 mg.

The combination of rifabutin and a proton pump inhibitor or bismuth preparation may be used in the treatment of gastrointenstinal disorders in a living being particularly a human.

In vitro bactericidal activity

Tests were carried out on several strains of *Helicobacter pylori* according to CZINN S. et al. Antimicrobial Agents Chemoter 30, 328-329, 1986 and Clinical

Microbiology Procedure Handbook, Isenberg H.D. ed. ASM 1992 (modified).

In the following tables is reported the activity of rifabutin, omeprazole and bismuth subcitrate sol (BSM) as single drug and in combination, on selected *H. pylori* strains.

The first example concerns the activity of rifabutin and BSM , the second one concerns the activity of rifabutin and omeprazole.

As shown in the tables, the inhibiting drug concentrations are lower when drugs are combined together.

Example 1

Combination of rifabutin and bismuth subcitrate sol.

Helibacter pylori strain 46.

rifabutin (μg/ml)	BSM (μg/ml)	effect
0.0037	-	MIC*
-	4	MIC
0.0009	0.5	SYN*
0.00045	1	SYN

Helicobacter pylori strain 34

rifabutin (μg/ml)	BSM (μg/ml)	effect
0.0075	-	MIC
-	4	MIC
0.0018	0.5	SYN
0.0009	1	SYN

Helicobacter pylori strain 13

rifabutin (µg/ml)	BSM (µg/ml)	effect
0.0075	-	MIC
-	2	MIC
0.0018	0.5	SYN

* MIC: minimal inhibitory concentration

** SYN: inhibited at subMIC concentrations

Example 2

Combination of rifabutin and omeprazole

Helicobacter pylori strain 35

rifabutin (µg/ml)	**omeprazole (µg/ml)**	**effect**
0.0037	-	MIC
-	64	MIC
0.0009	4	SYN
0.00045	16	SYN
0.00022	16	SYN

Helicobacter pylori strain 50

rifabutin (µg/ml)	**omeprazole (µg/ml)**	**effect**
0.0075	-	MIC
-	32	MIC
0.0018	4	SYN
0.0018	2	SYN
rifabutin (µg/ml)	**omeprazole (µg/ml)**	**effect**
0.0009	8	SYN

Helicobacter pylori strain 43

rifabutin (µg/ml)	omeprazole (µg/ml)	effect
0.0075	-	MIC
-	64	MIC
0.0018	2	SYN
0.0009	8	SYN
0.00045	16	SYN
0.00022	16	SYN

CLAIMS

1. A pharmaceutical composition suitable for use in the treatment of a *Helicobacter pylori* infection, which composition comprises:

(I) rifabutin; and

(II) a proton pump inhibitor or a bismuth preparation in a quantity producing a synergistic activity against *Helicobacter pylori*.

2. A pharmaceutical composition according to claim 1 further comprising a pharmaceutically acceptable carrier or diluent.

3. A pharmaceutical composition according to claim 1 or 2, wherein the proton pump inhibitor is selected from omeprazole, lansoprazole, leminoprazole, pantoprazole or robeprazole; or the bismuth preparation is selected from bismuth subsalicyclate or bismuth subcitrate sol (dried).

4. A pharmaceutical composition according to claim 3 wherein the proton pump inhibitor is omeprazole or the bismuth preparation is bismuth subcitrate sol (dried).

5. A process for preparing a pharmaceutical composition according to any one of claims 1 to 4, which process comprises mixing:

(I) rifabutin;

(II) a proton pump inhibitor or a bismuth preparation in a quantity producing a synergistic activity against

Helicobacter pylori; and

(III) optionally, a pharmaceutically acceptable carrier or diluent.

6. A pharmaceutical composition as defined in any one of claims 1 to 4 for use in the treatment of a *Helicobacter pylori* infection.

7. A pharmaceutical composition according to claim 6 for use in the treatment of gastritis or peptic ulcers.

8. Use, in the manufacture of a medicament for use in the treatment of a *Helicobacter pylori* infection, of:

(I) rifabutin; and

(II) a proton pump inhibitor or a bismuth preparation;

component (II) being present in an amount producing a synergistic activity against *Helicobacter pylori*.

9. The use according to claim 8 wherein the medicament is for use in the treatment of gastritis or peptic ulcers.

10. Products containing:

(I) rifabutin; and

(II) a proton pump inhibitor or a bismuth preparation in a quantity producing a synergistic activity against *Helicobacter pylori*;

as a combined preparation for simultaneous, separate or sequential use in the treatment of a *Helicobacter pylori* infection.

INTERNATIONAL SEARCH REPORT

Inten. .nal Application No
PCT/EP 96/02493

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K33/24 A61K31/445 A61K31/44 //(A61K33/24,31:445), (A61K31/445,31:44)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	J. ANTIMICROB. CHEMOTHER., vol. 35, no. 4, April 1995, ENGLAND, pages 545-549, XP000600927 J.HOLTON ET AL.: "the susceptibility of helicobacter pylori to the rifamycin rifaximin" *cf. page 545, introduction, 3rd para., page 546, 2nd and 3rd paras.* ---	1-10
Y	AM. JOURNAL OF GASTROENTEROL., vol. 89, no. 8, 1994, 1ST MED. CLIN. UNIV. BOLOGNA ITL, page 1382 XP000603245 M. MENEGATTI ET AL.: "rifaximin suspension for the eradication of helicobacter pylori" *cf. abstract no 389* ---	1-10

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[X] Further documents are listed in the continuation of box C. [ ] Patent family members are listed in annex.

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	CLIN. INFECTIOUS DISEASES, vol. 22, no. suppl. 1, 1996, UNIVERSITY OF CHICAGO, pages s3-s14, XP000600925 KUNIN, C. M.: "antimicrobial activity of rifabutin" *cf. abstract, page s9, left col., para. 5, right col., summary 1st para.*	1-10
Y	* see reference No 115 (Rossi et al.) *	1-10

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